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# Cavitands with Revolving Doors Regulate Binding Selectivities and Rates in Water

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Cavitands are concave hosts that bind small molecules of complementary size, shape, and chemical surface.[1] Deepened cavitands enclose most of a small guest, but the open end reduces the selectivity and exposes part of the guest to the external medium.[2] Exquisite selectivities can be achieved using capsules that completely surround the guest(s).[3−7] We report here an alternative in the form of new receptor: a cavitand with doors which can be rotated over the open end.

We recently described a water-soluble cavitand **1** that coaxes hydrophobic guests into the cavity where they are more or less shielded from the aqueous environment.[8] These complexes are kinetically stable; that is, exchange of guests is slow on the NMR time scale. The guests are surrounded by surfaces made of aromatic subunits, allowing for van der Waals interactions between host and guest. This attraction leads to conformational changes for normal hydrocarbons, such as hexane: they coil to make better contacts with the inner lining of the receptor and reduce the surfaces exposed to the aqueous environment.[9]

We prepared tetracarboxylate cavitand **2** in a manner analogous to that of **1**.[8] The octanitroarene **3**[10] was reduced to the corresponding octamine hydrochloride[11] and condensed with imidate **5** to give tetraester **7** in 55% overall yield. Treatment with NaOH in aqueous THF effected hydrolysis of the esters to give the desired tetrabenzoate cavitand **2**. Cavitand **2** shows good solubility in water, and the folded "vase" conformation is dominant at concentrations of 1 mM or below.

Cavitand **2** displays binding characteristics similar to those of **1**. Small hydrophobic species, such as cycloalkanes, can be extracted into the aqueous phase by **2**, forming 1:1 host−guest complexes.[9b] By $^1$H NMR analysis, only one host−guest species can be seen, and on the basis of the detection limits of the NMR spectrometer, this translates to a binding constant of $>10^4$ M$^{-1}$. With cyclopentane, cyclohexane, and cycloheptane, the guests tumble rapidly at room temperature, leading to an averaging of the chemical shifts to give one sharp singlet in the $^1$H NMR spectra in the far upfield region (Figure 2). Competition experiments show cyclopentane is preferentially bound with respect to cyclohexane by a ratio of 3:1, and cyclopentane is preferred over cycloheptane by 16:1. Under the same conditions, **1** preferred cyclohexane slightly over cyclopentane (1.3:1) and over cycloheptane (2:1). A direct competition experiment between the two cavitands was also performed (see Supporting Information). When 1 equiv of cyclopentane was exposed to a mixture of **1** and **2**, a binding $K_{rel}$ of 7.5 in favor of encapsulation in **2** was observed. However, when the same experiment was performed using cyclohexane, the $K_{rel}$ obtained was 2:1 in favor of binding in **1**. Evidently for **1**, cyclohexane fills the available space best, but cavitand **2** shows a selectivity for the smaller guests.

The origins of this selectivity can be understood through analysis of the downfield regions of the $^1$H NMR spectra (Figure 2). The characteristic signals for the aromatic protons $H_a$ and $H_b$ of the benzoates occur as only two sets of doublets. Free rotation of the benzoates ensures the structure is (time-averaged) symmetrical and each of them experiences the same averaged magnetic environment.

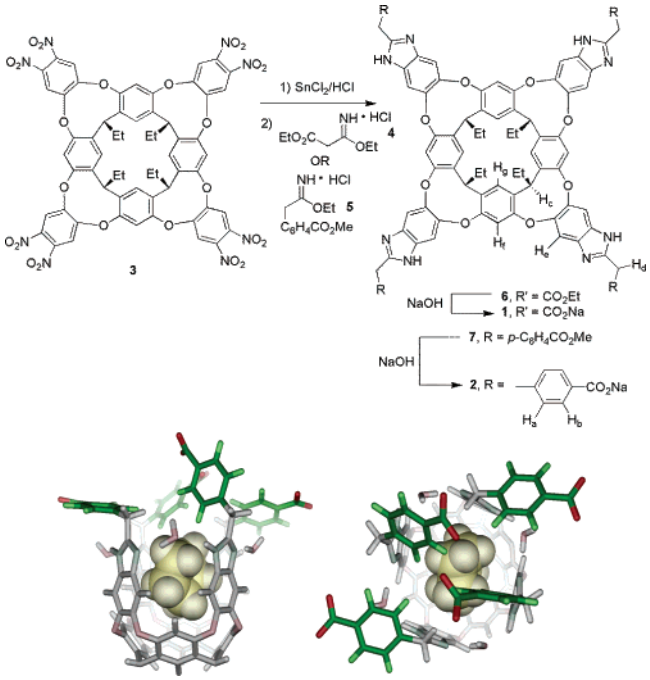


***Figure 1.*** (a) Syntheses of water-soluble tetracarboxylate cavitands **1** and **2** and (b) representations of the folded complex of **2** with cyclopentane indicating a resting position of the upper "revolving door" benzoate groups (Spartan; AM1 force field; some groups omitted for clarity).

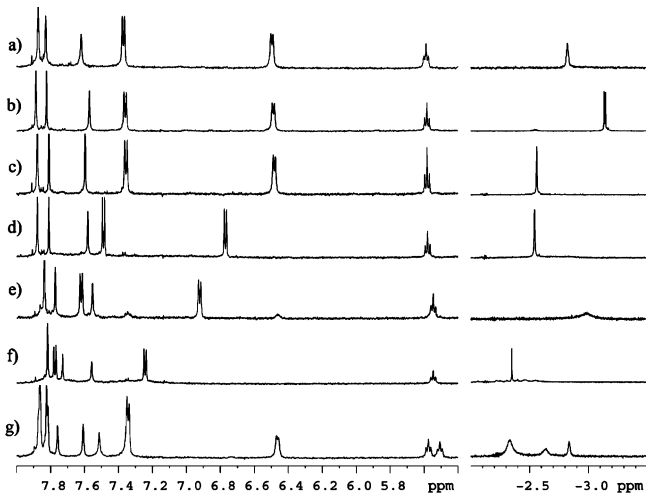


***Figure 2.*** Downfield and upfield regions of $^1$H NMR spectra of excess (a) THF; (b) isobutane; (c) cyclopentane; (d) cyclohexane; (e) *n*-pentane; (f) cycloheptane; and (g) *n*-hexane in a 1 mM solution of **2** in $D_2O$.



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The chemical shifts of $H_a$ and $H_b$ were unexpected. When **2** is occupied by one molecule of THF in its resting state (an artifact of the saponification solvent), the doublets occur at $\delta$ 6.50 and 7.37 ppm. The protons *meta* to the carboxylate groups ($H_a$) are shifted considerably upfield by the anisotropy of the cavity.[12] This positions them above the cavitand's open end with the C−H bonds directed into the cavity. The magnitude of the upfield shift ($\delta\Delta = -0.86$ ppm) is consistent with two benzoates, on average, above the opening (see Supporting Information and Figure 1b).

The position of these doors tracks with their chemical shifts and can be used as a measure of the relative size of an encapsulated guest. There is a limit for the position of the doors—the $^1$H NMR signals for cavitand with small guests, such as isobutane, tetrahydrofuran, and cyclopentane, are essentially identical; the fully closed doors show $H_a$ at 6.50 ppm. As the guest gets larger, the doors can no longer close onto the cavity due to steric clashes. The average location of the relevant protons is further from the anisotropy of the cavitand, the shielding effect is diminished, and the chemical shift moves downfield (Figure 2d−g). For example, binding of cyclohexane (see Figure 2d) causes the signals for $H_a$ to move downfield to 6.76 ppm, while leaving the other cavitand peaks ($H_c$−$H_g$) unchanged. Cycloheptane shifts $H_a$ even further to 7.27 ppm. *n*-Alkanes are longer than their cyclic counterparts, and so *n*-pentane opens the doors further than does cyclopentane or cyclohexane, and the binding of *n*-hexane causes the doors to fully open to the extent that no shielding of $H_a$ occurs. Encapsulation of longer guests, such as *trans*-decalin, shows cavitand signals similar to those of *n*-hexane. One additional change in the NMR spectra of **2** with larger guest is the shift of methine proton $H_c$ upfield, which generally occurs in systems similar to this when the walls are pushed outward.

Molecular modeling lends support to this proposal—semiempirical analysis of the complex between **2** and cyclopentane (Figure 1b) shows a resting state where two of the benzoate doors are situated directly above the cavitand, with the other two positioned outward in the bulk solvent. The barrier to rotation around the single bonds is very small, and hence at room temperature, these doors move rapidly on the NMR time scale.

Comparison of the chemical shifts observed for bound cycloalkane guest between **1** and **2** shows that for larger species where the lid is fully open (cycloheptane and cyclooctane) the shifts are very similar ($\delta$ −2.38:−2.34 and $\delta$ −2.07:−2.12, respectively). However, the closing of the lid causes a change—cyclopentane and cyclohexane are shifted *downfield* when bound in **2** as compared to **1** ($\delta$ −2.56:−2.86 and $\delta$ −2.54:−2.71 ppm, respectively). The orientation of the benzoate doors shown in Figure 1b is fully consistent with their effects on the guest: presentation of the benzoate edge to the guests causes deshielding as observed. If the doors presented their flat aromatic faces to the guests, shielding and further upfield shifts would result. A 2D NOESY spectrum of cyclopentane in a 1 mM solution of **2** in $D_2O$ shows NOE enhancements between protons $H_a$ and $H_b$ and the signal for encapsulated guest at −2.5 ppm (see Supporting Information). No NOE was detected between benzyl protons $H_d$ and guest.

When larger guests force the doors away from the cavitand, an energetic penalty is paid, increasing the selectivity for small guests. A change in guest size of only 2 carbons (~30 Å$^3$) from $C_5H_{10}$ to $C_7H_{14}$ causes a binding selectivity of 16:1. This effect also leads to a lower affinity for the binding of larger guests than **1**. It has been previously shown that **1** can bind long alkanes up to $C_{12}H_{26}$ in the cavity, but even a guest as small as *n*-hexane shows incomplete encapsulation by **2**, and *n*-octane is the longest alkane bound.

Apart from the selectivity conferred upon **2** by the doors, there are consequences for the exchange rate of guests into and out of the cavitand. Quantitative data through EXSY experiments have generally been thwarted by the low solubility of the hydrocarbons in $D_2O$, but some qualitative observations are possible. For example, the resident THF in cavitand **1** is only weakly bound in aqueous solution, and its NMR signals are exchange broadened. In contrast, **2** shows very sharp signals for bound THF, indicating that exchange in and out of its cavitand is slowed. Likewise, the spectrum of cyclopentane bound in **1** shows a broad peak due to intermediate rates of exchange but one sharp singlet when bound in **2** (Figure 2). A comparison of the rates of exchange of guests in the two cavitands **1** and **2** was possible by analysis of the integrals of the EXSY cross-peaks obtained in the 2D NOESY spectra of **1**·cyclohexane and **2**·cyclohexane (see Supporting Information).[13] Complex **1**·cyclohexane shows relatively rapid in/out rate constants of 25 and 150 $s^{-1}$, respectively, whereas the equivalent rate constants for **2**·cyclohexane are on the order of 100-fold smaller (0.6 and 0.8 $s^{-1}$, respectively), consistent with restricted guest exchange conferred upon **2** by the revolving doors.

In summary, a new water-soluble receptor has been prepared and characterized. Unlike the self-assembled capsules that fully surround their guests through metal ligand interactions,[3,4] salt bridges,[5] hydrogen bonds,[6] and even simple hydrophobic effects,[7] the new cavitands feature rotating doors attached to the open end. The doors increase selectivity for small guests, and binding constants exceed $10^4$ $M^{-1}$ with selectivity for cyclopentane over cycloheptane of about 16:1. The doors also reduce the rate of exchange of various small guests in and out of the cavitand. Further studies on the nature of this type of restricted-entrance receptor will be reported in the future.

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**Supporting Information Available:** Full experimental and characterization of new species and selected NMR data. This material is available free of charge via the Internet at http://pubs.acs.org.

## References

(1) (a) Cram, D. J.; Cram, J. M. In *Container Molecules and Their Guests*; Stoddart, F., Ed.; The Royal Society of Chemistry: London, 1994. (b) Cram, D. J.; Karbach, S.; Kim, H.-E.; Knobler, C. B.; Maverick, E. F.; Ericson, J. L.; Helgeson, R. C. *J. Am. Chem. Soc.* **1988**, *110*, 2229−2237. (c) Moran, J. R.; Ericson, J. L.; Dalcanale, E.; Bryant, J. A.; Knobler, C. B.; Cram, D. J. *J. Am. Chem. Soc.* **1991**, *113*, 5707−5714.
(2) Tucci, F. C.; Rudkevich, D. M.; Rebek, J. *J. Org. Chem.* **1999**, *64*, 4555−4559.
(3) Caulder, D. L.; Raymond, K. N. *Acc. Chem. Res.* **1999**, *32*, 975−982.
(4) (a) Fujita, M.; Umemoto, K.; Yoshizawa, M.; Fujita, N.; Kusukawa, T.; Biradha, K. *Chem. Commun.* **2001**, 509−518. (b) Harrison, R. G.; Burrows, J. L.; Hansen, L. D. *Chem.—Eur. J.* **2005**, *11*, 5881−5888.
(5) Corbellini, F.; Costanzo, L. D.; Crego-Calama, M.; Geremia, S.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **2003**, *125*, 9946−9947.
(6) Heinz, T.; Rudkevich, D. M.; Rebek, J. *Nature* **1998**, *394*, 764−766.
(7) Gibb, C. L. D.; Gibb, B. C. *J. Am. Chem. Soc.* **2004**, *126*, 11408−11409.
(8) Biros, S. M.; Ullrich, E. C.; Hof, F.; Trembleau, L.; Rebek, J. *J. Am. Chem. Soc.* **2004**, *126*, 2870−2876.
(9) (a) Trembleau, L.; Rebek, J. *Science* **2003**, *301*, 1219−1220. (b) Hooley, R. J.; Biros, S. M.; Rebek, J. *Chem. Commun.* **2006**, *5*, 509−510.
(10) Amrhein, P.; Shivanyuk, A.; Johnson, D. W.; Rebek, J. *J. Am. Chem. Soc.* **2002**, *124*, 10349−10358.
(11) Rafai Far, A.; Shivanyuk, A.; Rebek, J. *J. Am. Chem. Soc.* **2002**, *124*, 2854−2855.
(12) Menozzi, E.; Onagi, H.; Rheingold, A. L.; Rebek, J. *Eur. J. Org. Chem.* **2005**, *17*, 3633−3636.
(13) Zolnai, Z.; Juranic, N.; Vikic-Topic, D.; Macura, S. *J. Chem. Inf. Comput. Sci.* **2000**, *40*, 611−621.

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